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REMARKS

Claims 1, 6-22, and 24-47 are pending in the present application. Claims 2-5 and 23 have been canceled. Claims 36-47 are new. Applicants wish to than Examiner George withdrawing the restriction requirement and examining all claims in the application.

New claims 38, 40-47 recite compositions suitable for preventing or treating chronic obstructive pulmonary disease. The use the 13-*cis*-retinoic acid for treating COPD was described in the specification on p. 4, lines 30-33. New dependent claims 36, 37, 39 add the limitation that the compositions are inhalation formulations. The use of inhalation formulations is disclosed in the specification on p. 5, lines 2-9 and examples 3-5 on p. 15, line 22 to p. 16, line 29 of the patent application.

Claim 11 also was amended to distinctly point out that the method claims compositions that alleviate one or more of the symptoms of emphysema. On p. 13, lines 14-17 a "therapeutically effective amount" is defined as the amount necessary to alleviate the symptoms of emphysema. Thus no new matter is introduced by this amendments.

Claims 12, 13 and 23 were amended to correct improper dependencies and claims 29 and 30 were amended to correct typographical errors.

Claim 23 was objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to limit the subject matter of a previous claim. Claim 23 has been canceled.

Claims 1-10, 21, 22 and 24-34 are rejected under the judicially created doctrine of obvious-type double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 6,339,107 B1. After prosecution of the remaining claims is completed, applicants will file a terminal disclaimer in accordance with 37 CFR § 1.321(c). The present application is a divisional of US 6,339,107 and patent and application are assigned to Syntex (U.S.A.) LLC.

Claims 11-25 and 35 are rejected under 35 U.S.C. §103(a) as being unpatentable over Bollag *et al.* (EP 0 579 915 A1). Bollag *et al.* teach pharmaceutical compositions containing 9-*cis*- or 13-*cis*-retinoic acid in combination with a Vitamin D derivative. The use of the these compositions for treatment or prevention of tumors, pathological or undesired immune reactions, allergies asthma, psoriasis and osteoporosis are taught.

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> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.
>
> The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

MPEP 2143.02

Bollag does not teach the use of a *cis*-retinoic acid for treating emphysema or chronic obstructive pulmonary disease (COPD). These diseases are fundamentally different from all the diseases taught by Bollag. Bollag does not teach pulmonary administration of the compounds. Bollag teaches formulations for enteral, parenteral, oral and topical formulations. Moreover, Bollag teaches administration of combinations of retinoic acid and vitamin D derivatives.

No motivation to prepare pharmaceutical compositions, much less inhalation formulations, of *cis*-retinoic for treating emphysema or COPD exist in the prior art. Absent teaching of the use of *cis*-retinoic for treating emphysema or COPD there also is no expectation of success.

> To establish *prima facie* obviousness of a claimed invention all the claim limitations must be taught or suggested by the prior art. *In re Royka* 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words of a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson* 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970).

MPEP §2143.03

Claims 11 and 35 contain the limitations "suitable for treating a mammal suffering from emphysema" and " suitable for preventing emphysema". New claim 38 contains the limitation "composition for treating a mammal suffering from chronic obstructive pulmonary disease" The prior art neither teaches nor suggests these claim limitations.

Applicants respectfully submit that the requirements for a *prima facie* case have not been met and withdrawal of the rejection is respectfully requested.

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CONCLUSION

Applicants believe the new and amended claims are in condition for allowance and favorable consideration and passage of the claims to issuance is respectfully requested. A clean copy of the claims is attached in the Appendix A. A clean copy of the amendment to the specification is attached in Appendix B.

Applicants believe no fee is due with this response; however, should it be determined that a fee is required please charge them to Deposit Account No. 18-1700 (Roche Palo Alto). A copy of Canadian application No. 2,096,196 which is believed to be exact English language translation of EP 0 579 915 A1 is enclosed for the Examiner's convenience. If the Examiner believes that an interview will advance prosecution or aid in the favorable consideration of this amendment, the Examiner is respectfully invited to contact the applicant's representative.

Respectfully submitted,
Roche Palo Alto LLC

_____
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Enclosures:

Copy of Canadian Application 2,096,196 (translation of EP 0 579 915 A1)

Consommation et Affaires commerciales Canada
Bureau des brevets
Ottawa, Canada
K1A 0C9

Consumer and Corporate Affairs Canada
Patent Office

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(19)(CA) APPLICATION FOR CANADIAN PATENT (12)

(54) Pharmaceutical Compositions

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(30) (CH) 1619/92 1992/05/20
(CH) 926/93 1993/03/26

(57) 14 Claims

RAN 4051/28

2096196

Abstract

Pharmaceutical preparation containing 9-cis- or 13-cis retinoic acid, or acitretin, a pharmaceutically usable salt or ester thereof and a vitamin D derivative as active ingredients, and usual pharmaceutical carriers.

The present invention is concerned with pharmaceutical preparations containing 9-cis- or 13-cis-retinoic acid or acitretin (all(E)-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoic acid), a pharmaceutically usable salt or ester thereof and a vitamin D derivative. It has been found that such preparations can be used for the treatment of psoriasis, of osteoporosis, of precanceroses and of tumours, as well as for the treatment of pathological or undesired immune reactions. The invention is therefore also concerned with the use of 9-cis-or 13-cis-retinoic acid or acitretin, pharmaceutically usable salts or esters thereof for the combined use with vitamin D derivatives in the treatment of the said diseases and anomalies. Finally, the invention is concerned with the use of 9-cis-or 13-cis-retinoic acid or acitretin, pharmaceutically usable salts or esters thereof in the manufacture of pharmaceutical preparations for the combined use with vitamin D derivatives in the treatment of the aforementioned diseases and anomalies.

Examples of pharmaceutically usable salts of 9-cis- or 13-cis-retinoic acid or acitretin are alkali salts such as the Na and K salt, alkaline earth metal salts such as the Ca and Mg salt; as well as the ammonium salt and alkylammonium salts. Examples of esters are lower-alkyl esters such as the methyl and ethyl ester such as etretinate, and aromatic esters such as the benzyl ester.

Examples of vitamin D derivatives which can be used in accordance with the invention are hydroxylated vitamin D_3 derivatives such as 1α-hydroxy-vitamin D_3, 1α,25-dihydroxy-vitamin D_3 (calcitriol), 1α,25,26-trihydroxy-vitamin D_3, 1α,23,25-trihydroxy-vitamin D_3, 24-fluoro-1α,25-dihydroxy-vitamin D_3, 24,24-difluoro-1α,25-dihydroxy-vitamin D_3, 26,26,26-trifluoro-1α,25-dihydroxy-vitamin D_3, 26,26,26,27,27,27-hexafluoro-1α,25-dihydroxy-vitamin D_3; 1α,25-dihydroxy-22,23-dehydro-vitamin D_3, 26,26,26-trisdeutero-22,23-dehydro-1α,25-dihydroxy-vitamin D_3, 26,26,26,27,27,27-hexakisdeutero-22,23-dehydro-1α,25-dihydroxy-

vitamin D_3, 26,26,26-trifluoro-1α,25-dihydroxy-22,23-dehydro-vitamin D_3, 26,26,26,27,27,27-hexafluoro-1α,25-dihydroxy-22,23-dehydro-vitamin D_3, 26,26,26,27,27,27-hexafluoro-1α,25-dihydroxy-23,24-dehydro-vitamin D_3, 1α,25-dihydroxy-vitamin D_2, 26,26,26,27,27,27-hexakisdeutero-1α,25-vitamin D_2, 1α,25-dihydroxy-27-nor-vitamin D_2, 1α,25,26-trihydroxy-22,23-dehydro-vitamin D_3, 1α,25,26-trihydroxy-vitamin D_2, 1α,25-dihydroxy-23,24-didehydro-vitamin D_3, 1α,25-dihydroxy-16,17-dehydro-vitamin D_3, 1α,25-dihydroxy-16,17;23,24-bisdehydro-vitamin D_3, 1α,25-dihydroxy-16,17-dehydro-23,24-didehydro-vitamin D_3, 26,26,26,27,27,27-hexafluoro-1α,25-dihydroxy-16,17-dehydro-23,24-didehydro-vitamin D_3, 1α,26,26,26,27,27,27-heptafluoro-25-hydroxy-23,24-didehydro-vitamin D_3, 1α,25-dihydroxy-3-deoxy-23,24-didehydro-vitamin D_3 and 25-hydroxy-23,24-didehydro-vitamin D_2.

The aforementioned vitamin D derivatives and their preparation are known, see, e.g., the US patent specifications 3 993 675, 4 022 768, 4 407 754, 4 421 690, 4 594 432, 4 594 346, 4 612 308, 4 613 594, 4 652 405, 4 749 710, 4 804 502, 4 898 855, 4 906 785, 4 929 609, 5 087 619 and 5 120 722.

26,26,26,27,27,27-Hexafluoro-1α,25-dihydroxy-16,17-dehydro-23,24-didehydro vitamin D_3 has not yet been described and can be obtained as follows:

A. To 522 mg of [3aS-[3(S*),3aα,7α,7aβ]]-[[3a,4,5,6,7,7a-hexahydro-3a-methyl-3-(1-methyl-3-butynyl)-1H-inden-7-yl]oxy]trimethylsilane in 15 ml of anhydrous tetrahydrofuran, 1.85 ml of 1.6M solution of n-butyllithium in hexane was added dropwise after cooling at -75°C over 5 minutes and the mixture was stirred at -75°C for 30 min. Then a stream of hexafluoroacetone was bubbled into the mixture for 15 min with temperature maintained at -75°C. The reaction mixture was stirred for one additional hour, and then quenched with 1:1 mixture of 2M $KHCO_3$ and 1M Rochelle salt added dropwise. The mixture was stirred at room temperature for one hour and then diluted with 25 ml of the same salt solution. After

extraction with CH_2Cl_2, the organic phase was washed with 50 ml of the same salt solution, dried and evaporated. The residue was azeotroped with benzene to give 2.38 g of crude oily product. Purification was performed by flash chromatography (EtOAc-hexane 1:9) to give 817 mg of [3aS-[3(S*),3[3aα,7α,7aβ]]-1,1,1-trifluoro-6[3a,4,5,6,7,7a-hexahydro-3a-methyl-7-[(trimethylsilyl)oxy]-1H-inden-3-yl]-2-(trifluoro-methyl)-3-heptyn-2-ol.

B. To a solution of 812 mg of [3aS-[3(S*),3aα,7a,7aβ]]-1,1,1-trifluoro-6[3a,4,5,6,7,7a-hexahydro-3a-methyl-7-[(trimethylsilyl)-oxy]-1H-inden-3-yl]-2-(trifluoromethyl)-3-heptin-2-ol in 18 ml of anhydrous tetrahydrofuran there was added 5.34 ml of tetra-butyl-ammonium fluoride in tetrahydrofuran, and the mixture was stirred at room temperature under argon for 80 min. The reaction was then quenched by addition of 9 ml of half-saturated $NaHCO_3$ and stirred at room temperature for an additional 20 min. Excess of tetrahydro-furan was removed by evaporation and additional 9 ml of bicarbonate was added. The mixture was extracted with ethyl acetate, the extract was washed with brine, dried and evaporated. After purification by flash chromatography (EtOAc-hexane 1:2), it gave 690 mg of [3aR-[1(R*),3aα,4β,7aβ]]-3,3a,5,6,7,7a-hexahydro-7a-methyl-1-[6,6,6-trifluoro-5-hydroxy-1-methyl-5-(trifluoro-methyl)-3-hexynyl]-4H-inden-4-ol.

C. To a solution of 100 mg of [3aR,-[1(R*),3aα,4β,7aβ]]-3,3a,5,6,7,7a-hexahydro-7a-methyl-1-[6,6,6-trifluoro-5-hydroxy-1-methyl-5-(trifluoromethyl)-3-hexynyl]-4H-inden-4-ol in 6 ml of anhydrous CH_2Cl_2 there was added at room temperature, 176 mg of pyridinium chlorochromate, and the mixture was stirred at room temperature for 50 min under argon. To this mixture there was added 9 ml of ether under stirring, then it was filtered and the filtrate evaporated to dryness. The crude product thus obtained was purified by chromatography on silicagel column with ethyl acetate-hexane 1:3 to give [3aR-[1(R*),3aα,7aβ]]-3,3a,5,6,7,7a-hexahydro-7a-methyl-1-[6,6,6-trifluoro-5-hydroxy-1-methyl-5-(trifluoro-methyl)-3-hexinyl]-4H-inden-4-one.

D. To a solution of 333 mg of [3S-(3α,5β,Z)]-2-[2-[2-methylene-3,5-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]cyclohexylidene]-ethyl]diphenyl phosphine oxide in 7 ml anhydrous tetrahydrofuran there was added at -75°C, 0.325 ml of 1.6M n-butyllithium in hexane under argon. After stirring for 6 min, a solution of 73 mg of [3aR-[1(R*),3aα,7aβ]]-3,3a,5,6,7,7a-hexahydro-7a-methyl-1-[6,6,6-trifluoro-5-hydroxy-1-methyl-5-(trifluoromethyl)-3-hexinyl]-4H-inden-4-one in 5 ml anhydrous tetrahydrofuran was added dropwise. The reaction mixture was stirred for 1 hour at -75°C, and then quenched with 2.6 ml of 1:1 mixture of 2N Rochelle salt and 2N $KHCO_3$ solutions and was allowed to warm to room temperature. It was then diluted with 10 ml of the same salt solution and extracted with ethyl acetate. The extract was washed with brine, dried and evaporated. The crude intermediate was purified by flash chromatography on silica gel column with ethyl acetate-hexane 1:5 to give disilyl-protected 1,25-dihydroxy-16-ene-23-yne-26,27-hexafluoro-cholecalciferol.

E. To 92 mg of the disilyl protected 1,25-dihydroxy-16-ene-23-yne-26,27-hexafluoro-cholecalciferol in 5 ml anhydrous tetrahydrofuran in a dark wall flask there was added 0.89 ml of 1M tetrabutylammonium fluoride in tetrahydrofuran, and the mixture was stirred for 16 hrs under argon. The reaction was then quenched with 3 ml of half-saturated $NaHCO_3$ and stirred at room temperature. It was then extracted with ethyl acetate. The extract was washed with half-saturated $NaHCO_3$ and brine, then dried and evaporated. The crude product was purified by flash chromatography with ethyl-acetate 4:1, to give 1,25-dihydroxy-16-ene-23-yne-26,27-hexafluoro-cholecalciferol as a foamy glass: $[\alpha]_D^{23}$ = +59.1° (c 0.11, CH_3OH).

In accordance with the invention the 9-cis- or 13-cis-retinoic acid or acitretin or a salt or ester thereof can be used in the form of pharmaceutical preparations which also contain a vitamin D derivative or as preparations which contain an ad hoc combination with vitamin D derivatives.

The use of 9-cis-retinoic acid, pharmaceutically usable salts or esters thereof and vitamin D derivatives, especially 9-cis-retinoic acid and calciferol is preferred.

The active substances can be administered topically or orally for the treatment of psoriasis. Topical preparations can be present as creams, ointments, lotions, tinctures or gels which contain the active substances together with carriers which are usual in such preparations. The content of 9-cis- or 13-cis-retinoic acid or acitretin, salts or esters thereof in these preparations can be about 0.001-0.1 wt.%, preferably 0.003-0.03 wt.%. The content of vitamin D derivative in such preparations can be about 1 µg/g to about 100 µg/g. These preparations are applied to the diseased site on the skin according to the requirements of the patient, e.g. once or twice per day.

Preparations for oral administration can be present in the form of tablets, capsules, solutions or emulsions. For the treatment of psoriasis, such preparations can be administered in dosages of about 0.01 mg to about 3 mg of 9-cis-or 13-cis-retinoic acid or acitretin or salt or ester thereof per kg body weight per day, preferably about 0.025 mg/kg to about 1.5 mg/kg per day; and about 0.001 µg/kg to about 0.1 µg/kg of vitamin D derivative, preferably about 0.005 µg/kg to about 0.05 µg/kg, per day. Solid dosage forms such as tablets and capsules conveniently contain per dosage unit about 1 mg to about 50 mg of 9-cis- or 13-cis-retinoic acid or acitretin and, respectively, about 0.1 µg to about 1 µg of vitamin D derivative.

For the treatment and prevention of tumours, the active substances or the preparations in accordance with the invention can be administered enterally, parenterally or topically. Examples of tumours which can be treated with the preparations in accordance with the invention or the active substance combination in accordance with the invention are haematological tumours such as leukaemia, especially acute promyelocytaric leukaemia and lymphomas. Furthermore precancerous lesions of the epithelial tissue such as actinic keratoses of the skin, oral leukoplakias,

dysplasias of the larynx, bronchi and cervix; as well as carcinomas of the skin, buccal cavity, the bronchi, the larynx, pharynx, stomach, colon, uterus, pancreas, the bladder, breast and prostate can be treated by the administration of an effective amount of the preparations or active substance combination in accordance with the invention.

Examples of pathological or undesired immune reactions are autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, insulin-dependent diabetes, lupus erythematosus, pemphigus vulgaris, pemphigus foliaceus, myasthenia gravis, ankylosing spondylitis, autoimmune diseases of the thyroid gland such as Hashimoto's disease and primary thyroid gland failure; scleroderma, uveitis, Behcet's disease, Crohn's disease, auto-immune-conditioned myocarditis and autoimmune-conditioned poly-glandular syndrome; as well as allergies such as allergic rhinitis, atopic dermatitis, asthma and celiaca. Other indications are undesired immune reactions in organ or cell transplants such as kidney, heart, pancreas beta-islet cell, bone marrow and liver transplants.

A further aspect of the invention is concerned with the use of the preparations and, respectively, active substance combination in accordance with the invention for the preferably enteral or parenteral treatment and prevention of osteoporosis. In all of these indications the active substances can be used in the dosage ranges given above, whereby the individual dosage will depend on the nature of the disease to be treated and on the age and condition of the patient and can be determined within the framework of medical expertise. The invention is illustrated in more detail by the following Examples.

Example 1

Capsules containing 9-cis-retinoic acid

9-cis-Retinoic acid	20.0 mg
Gelatine (Bloom number 30)	70.0 mg
Maltodextrin	108.0 mg
dl-α-Tocopherol	2.0 mg
Na ascorbate	10.0 mg
Microcrystalline cellulose	48.0 mg
Mg stearate	2.0 mg
Total	260 mg

The active substance is wet-ground in a solution of gelatine, maltodextrin, tocopherol and Na ascorbate and the suspension obtained is spray-dried. Thereafter, the cellulose and the Mg stearate are admixed and 260 mg aliquots of the mixture are filled into hard gelatine capsules.

Example 2

Capsules containing calcitriol

Calcitriol	0.25 µg
Butylated hydroxytoluene	0.016 mg
Buylated hydroxyanisole	0.016 mg
Fractionated coconut oil	ad 160.0 mg

The ingredients are mixed and the oily solution is filled under an inert gas into soft gelatine capsules each containing 160 mg.

Example 3

Capsules containing 9-cis-retinoic acid and calcitriol

Calcitriol	0.25 µg
9-cis-Retinoic acid	20 mg
Polyethylene glycol 400	200 mg
Butylated hydroxyanisole	0.1 mg

The ingredients are mixed and filled under an inert gas into soft gelatine capsules having a fill weight of 220 mg.

Example 4

Cream containing 9-cis-retinoic acid and calcitriol

Calcitriol	2 mg
9-cis-Retinoic acid	30 mg
Cetyl alcohol	1.5 mg
Stearyl alcohol	2.5 mg
Sorbitan monostearate	2.0 mg
Glyceryl monostearate and polyoxyethylene glycolstearate	4.0 mg
Polysorbate 60	1.0 mg
Mineral oil	4.0 mg
Propylene glycol	5.0 mg
Propylparaben	0.05 mg
Butylated hydroxyanisole	0.05 mg
Sorbitol solution	2.0 mg
Na EDTA	0.01 mg
Methylparaben	0.18 mg
Dist. water	q.s. ad 100 g

Example 5

The activity of the combination in accordance with the invention of 9-cis-retinoic acid and calcitriol on the differentiation of human promyelocytic leukaemia cells (HL-60) can be

demonstrated in vitro in the test procedure described in Cancer Research 45, 4244 (1985). The effects obtained with various concentrations of the active substances on cell differentiation (measured by detecting the reduction effect on nitrobiue-tetrazolium, NBT) can be concluded from Figure 1. The measurement of the NBT reduction was effected according to a modified method of Pick et al. in J. Reticul. Soc. 30, 581 (1981). In each case, $3 \cdot 10^4$ cells in 200 µl were incubated for 48 hours with the active substances. The cells were centrifuged off and treated with in each case 100 µl of pre-warmed NBT solution (1 mg/ml, diluted with Dulbeccos PBS) and PMA (123 mg/ml in DMSO) and incubated at 37°C for 1 hour. After centrifugation, 100 µl of 90% DMF, diluted with 10% SDS, were added, the mixture was incubated at 37°C and the extinction (OD) was measured at 550 mm.

The curves in Fig. 1 show the effect of calcitriol alone and of combinations of varying amounts of calcitriol with (from above downwards) 80 nM, 16 nM and 3.2 nM 9-cis-retinoic acid.

Example 6

Patients with multiple actinic keratoses were treated topically with 9-cis-retinoic acid and calcitriol. 9-cis-retinoic acid was applied as a 0.01% (v/v) solution in ethanol/propylene glycol (50:50). Calcitriol was applied as a 0.0025% (w/w) cream. Treatment was carried out for 4-16 weeks with administration of the preparations to the skin once daily. 9-cis-retinoic acid was applied first, followed, after drying (3 minutes), by calcitriol cream. Occlusive dressing was not used.

The following results were obtained with various patient groups:

A. Patient group: 16 patients
Duration of treatment: 4 weeks
Result of treatment:
6 patients: slight improvement
5 patients: moderate improvement
5 patients: marked improvement

B. Patient group: 16 patients
Duration of treatment: 8 weeks
Result of treatment:
3 patients: slight improvement
4 patients: moderate improvement
9 patients: marked improvement

C. Patient group: 7 patients
Duration of treatment: 12 weeks
Result of treatment:
in all 7 patients: marked improvement

D. Patient group: 3 patients
Duration of treatment: 16 weeks
Result of treatment:
in all 3 patients: marked improvement

In all cases, slight erythema but no disturbing symptoms (burning, itching) developed.

Patent Claims

1. Pharmaceutical preparation containing 9-cis- or 13-cis retinoic acid, or acitretin, a pharmaceutically usable salt or ester thereof and a vitamin D derivative as active ingredients, and usual pharmaceutical carriers.

2. A preparation according to claim 1, wherein the active ingredients are 9-cis retinoic acid, a pharmaceutically usable salt or ester thereof and a vitamin D derivative.

3. A preparation according to claim 2, wherein the active ingredients are 9-cis retinoic acid and calcitriol.

4. A product containing 9-cis- or 13-cis retinoic acid or acitretin, a pharmaceutically usable salt or ester thereof and a vitamin D derivative as a combination preparation for the simultaneous, separate or sequential use in the treatment of psoriasis, osteoporosis or tumours.

5. A product according to claim 4 for use in the treatment of pathological or undesired immune reactions.

6. A product according to claim 4 or 5 containing 9-cis retinoic acid and calcitriol.

7. A commercial pack containing 9-cis- or 13-cis retinoic acid, or acitretin, a pharmaceutically usable salt or ester thereof as active ingredients, together with instructions for the use thereof in combination with a vitamin D derivative for the simultaneous, separate or sequential use in the treatment of psoriasis, osteoporosis or tumours.

8. A commercial pack according to claim 7 for use in the treatment of pathological or undesired immune reactions.

9. A commercial pack according to claim 7 or 8 containing 9-cis retinoic acid together with instructions for the combined use with calcitriol.

10. 9-cis- or 13-cis retinoic acid or acitretin, a pharmaceutically usable salt or ester thereof and a vitamin D derivative for use as a medicament.

11. 9-cis retinoic acid and calcitriol for use according to claim 10.

12. The use of 9-cis- or 13-cis retinoic acid, or acitretin, a pharmaceutically usable salt or ester thereof in the manufacture of pharmaceutical preparations for the combined application with a vitamin D derivative in the treatment of psoriasis, osteoporosis or tumours.

13. The use according to claim 12 in the treatment of pathological or undesired immune reactions.

14. The use of 9-cis retinoic acid for the combined application with calcitriol according to claims 12 or 13.

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Differentiation of HL 60 cells by 9-cis retinoic acid and calcitriol

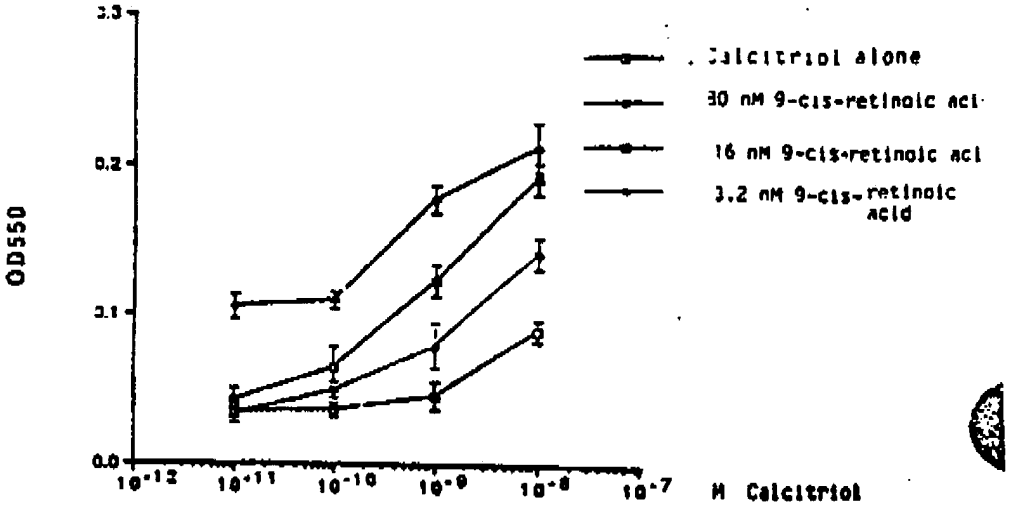

Figure 1